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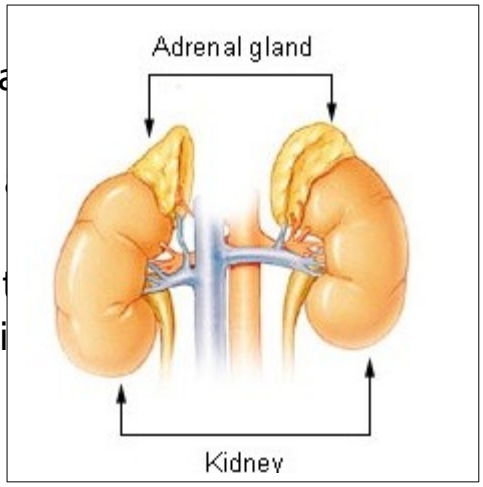
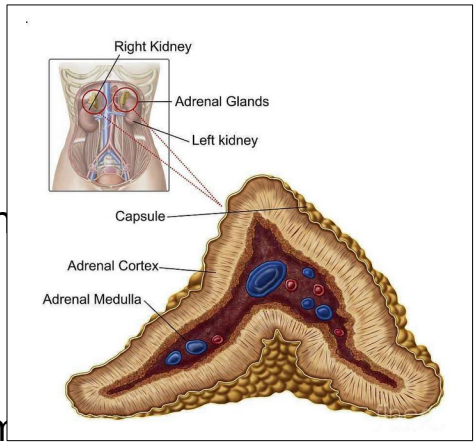
Adrenal Glands

- There are two pyramid-shaped organs, one on top of each kidney called adrenal (suprarenal) glands.
- Each gland consists of two parts an outer cortex and inner medulla which are structurally and functionally quite different.
- They are actually 2 endocrine glands:
  1- The cortex secrets different adrenocortica hormones which are essential for life while the medulla secretes catecholamines which NOT essential for life.
  2- The cortex is under anterior pituitary cont (ACTH), while the medulla is NOT under pi control (sympathetic division of ANS).



➢Structure:



1- **The adrenal cortex:** (outer part)
   It constitutes about 80% of the gland.
   It is divided into 3 zones.
   Each of these regions produces its own set of h
2- **Adrenal medulla:** (inner part)
   It constitutes about 20% of the gland.
   It is made up of nervous tissue and acts as part of the sympathetic nervous system
   It Secretes catecholamines: epinephrine, norepinephrine and dopamine.

The adrenal

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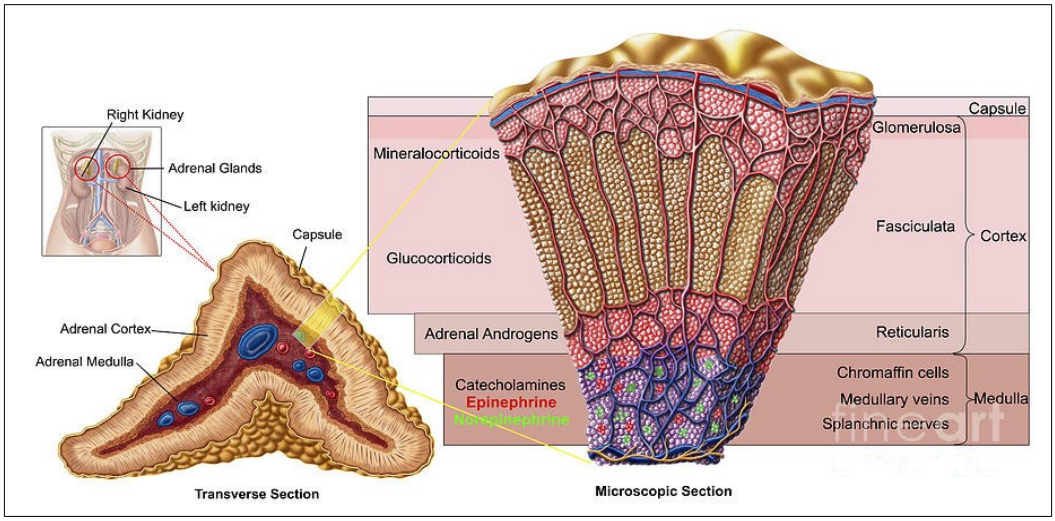
- It forms the outer part (80% of the gland). It is divided into three different layers or zones.



1- **Zona glomerulosa** (the outer most layer, 15 %). This zone secretes **mineralocorticoids** that control the metabolism of minerals. The main mineralocorticoid secreted is *aldosterone*.
2- **Zona fasciculata** (the middlle and largest portion, 50%). This zone secretes **glucocorticoids** that control glucose metabolism as well as protein and lipid metabolism. The main glucocorticoid secreted is *cortisol*.
3- **Zona reticularis** (the inner most layer, 7%). This zone secretes **sex hormones.** The main one is *androgens* and estrogen .They are present in both sexes.

- The hormones of the adrenal cortex are derivatives of cholesterol.
- Innumerable steroids have been isolated from adrenal tissue, but the only steroids normally secreted in physiologically significant amounts are the mineralocorticoid **aldosterone,** the glucocorticoids **cortisol** and **corticosterone,** and the androgens **dehydroepiandrosterone (DHEA)** and **androstenedione**.

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Deoxycorticosterone is a mineralocorticoid that is normally secreted in about the same amount as aldosterone but has only 3% of the mineralocorticoid activity of aldosterone.

N.B:

- *The adrenocortical cells contain abundant lipid, especially in the outer portion of the zona fasciculata.*
- *All three cortical zones secrete **corticosterone,** but the active enzymatic mechanism for aldosterone biosynthesis is limited to the zona glomerulosa, whereas the enzymatic mechanisms for forming cortisol and sex hormones are found in the two inner zones.*
- *Furthermore, subspecialization occurs within the inner two zones, the zona fasciculata, secreting mostly glucocorticoids*

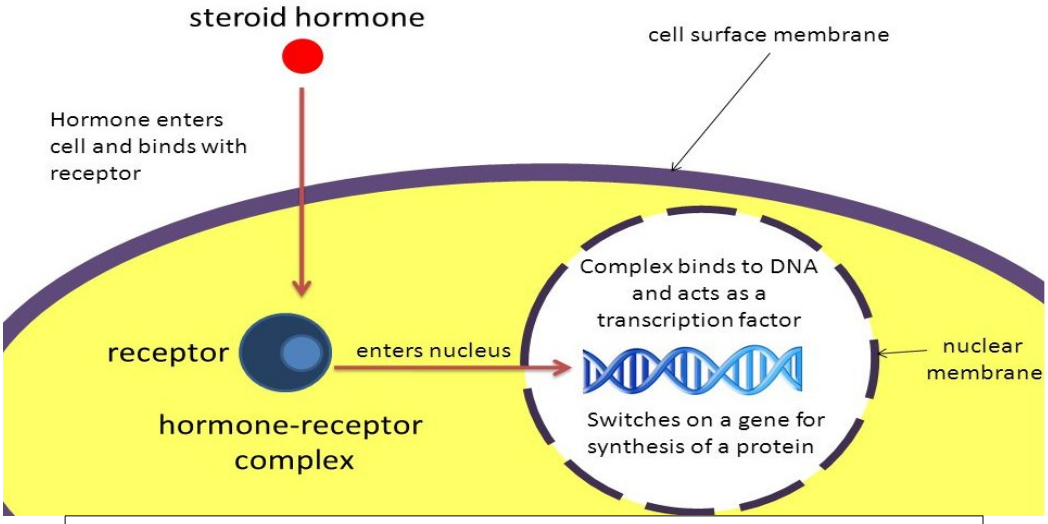
Mineralocorticoids

- They are essential for life.
- They are secreted by the zona glomerulosa of adrenal cortex.
- Aldosterone is the most potent and accounts for more than 95% of production. (deoxycorticosterone also is secreted).

- Aldosterone is bound to protein to only a slight extent, and the total plasma aldosterone level in humans is normally about 0.006 g/dL.

Mechanism of action:

1. Aldosterone is a lipophilic hormone (steroid hormone), diffuses readily to the inside of renal tubular cells.
2. In the cytoplasm, it combines with a specific receptor forming aldosterone – receptor complex which diffuses into the nucleus.
3. In the nucleus it initiates the formation of new proteins, mRNA formed and diffuse back to the cytoplasm.
4. The new proteins may be ***sodium channels*** or enzymes such as ***sodium-potassium dependent ATPase***, which pumps sodium out of the tubular cells into the interstitium.



Mechanism of action of steroid hormones

Physiological actions:

- The primary target organs of aldosterone are the principal cells (P cells) of the collecting ductsdistal tubules of the kidney.

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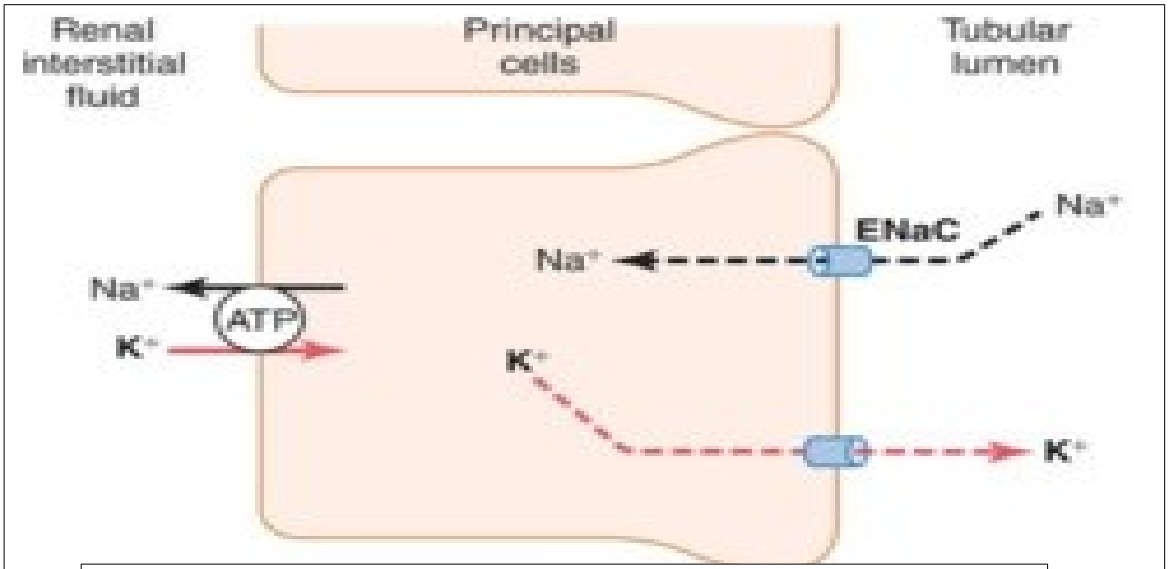
- It acts mainly to:
  1- Increase Na^+ reabsorption with subsequent Cl^-, bicarbonate and water reabsorption (by increasing the epithelial Na+ channels = ENaCs). This expands ECF volume.
  2- Increase K^+ and H^+ excretion (by increasing Na-K ATPase enzyme).
- It also increases the reabsorption of Na^+ from the urine, sweat, saliva, and the colon.



Action of aldosterone on principle cells in renal

Regulation of aldosterone:

1- **Potassium ion concentration in ECF:** Hyperkalemia has a direct stimulatory effect on the adrenal cortex.
2- **Sodium ion concentration**: Hyponatremia stimulates aldosterone secretion.

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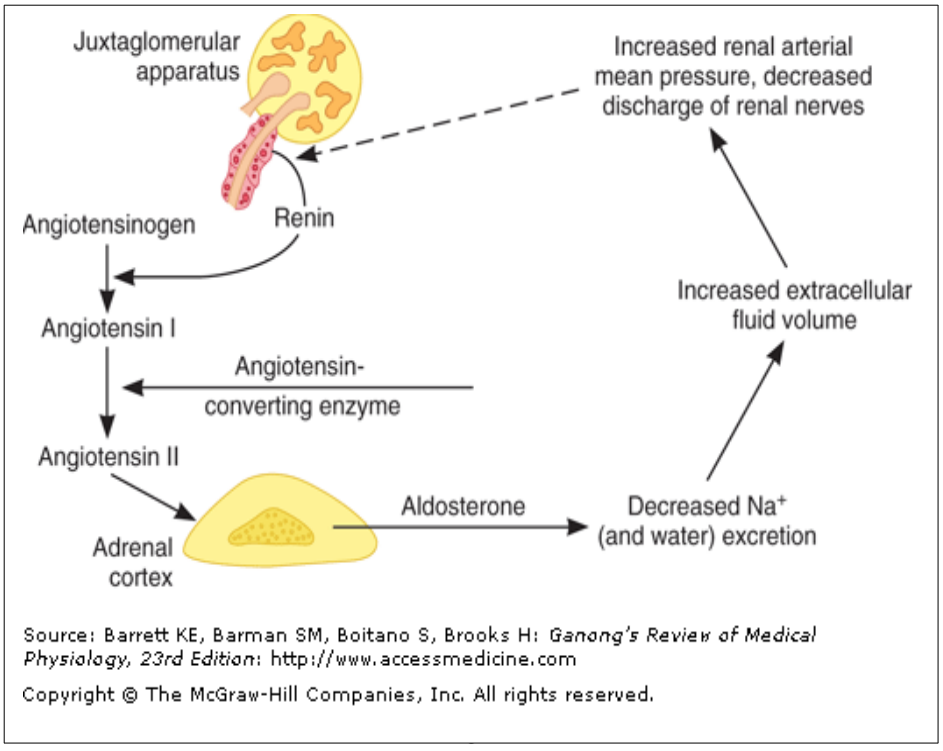
Aldosterone is more sensitive to increased K+ than to decreased Na+ level

3- **Renin-angiotensin system**. Aldosterone secretion is regulated via the renin–angiotensin system in a feedback fashion. A drop in ECF volume or intra-arterial vascular volume leads to a reflex increase in renal nerve discharge and decreases renal arterial pressure. Both changes increase renin secretion, and the angiotensin II formed by the action of the renin increases the rate of secretion of aldosterone. The aldosterone causes Na^+ and, secondarily, water retention, expanding ECF volume and shutting off the stimulus that initiated increased renin secretion.

4- **Pituitary control through ACTH**: Although aldosterone secretion is independent of the anterior pituitary control, ACTH has a small stimulant effect on the release of aldosterone especially in stress).

5- Atrial natriuretic peptide (ANP): inhibits aldosterone synthesis.



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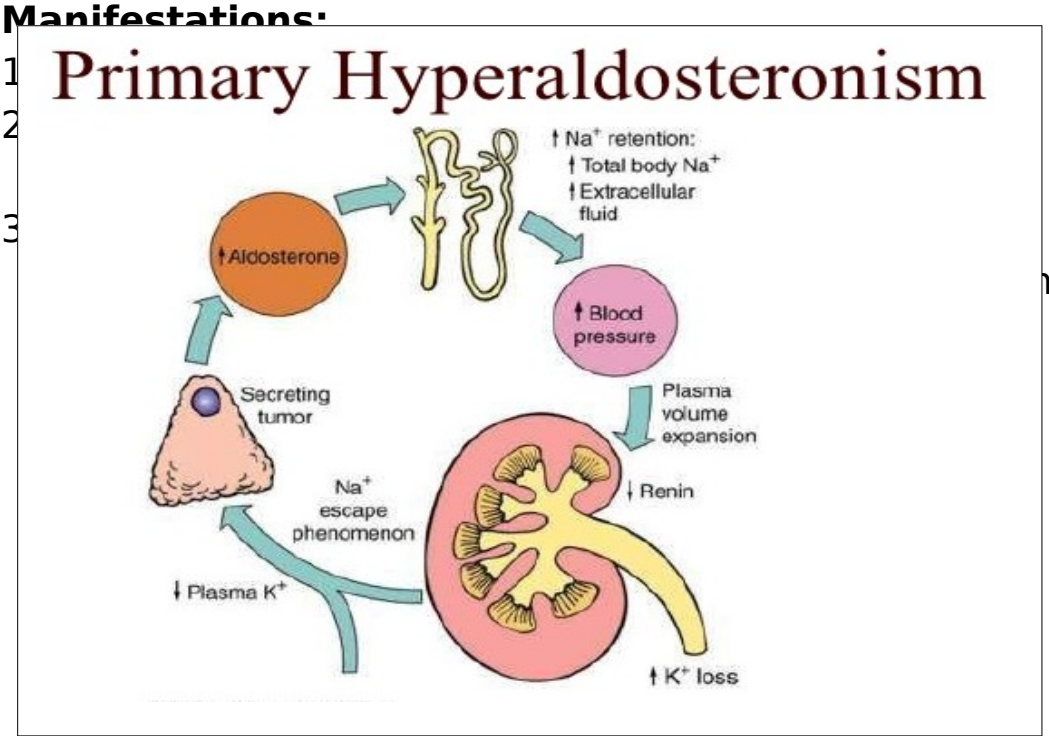
Feedback mechanism regulating aldosterone secretion

- **<u>Disorders of aldosterone hormone secretion :</u>**
  - Excess aldosterone secretion may be:
    1- Primary hyperaldosteronism (Conn's disease): adenoma in the zona glomerulosa.
    2- Secondary hyperaldosteronism due to increased activity of renin-angiotensin system (may be due to decreased renal blood flow).
  - Deficiency of aldosterone hormone: see Addison 's disease.

Primary hyperaldosteronism

- **Cause:** Due to tumor of the zona glomerulosa cells.
- **Manifestations:**
  1
  2
  3



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Glucocorticoids (Cortisol)

- They are absolutely essential for life.
- Glucocorticoids are secreted by zona fasciculata.
- Cortisol (hydrocortisone) has 95% of all glucocorticoid activity. Corticosterone (less potent).
- The total plasma cortisol level is **13.5 µg/dL**.
- 75 % of cortisol circulates bound to corticosteroid binding globulin (transcortin), less amount bound to albumin. 10 % of cortisol is free.

- **Mechanism of action:**

- Glucocorticoids are lipophilic hormones (steroid in nature).
- The multiple effects of glucocorticoids are triggered by binding to glucocorticoid receptors (cytoplasmic receptors), and the steroid–receptor complexes act to promote the transcription of certain segments of DNA. This, in turn, leads via the appropriate mRNAs to synthesis of enzymes that alter cell function.

- **Physiological actions of glucocorticoids (cortisol):**

1- Effect on intermediary metabolism:

- Glucocorticoids act on the intermediary metabolism as carbohydrate, protein, and fat. Their actions include increased protein catabolism and increased hepatic glycogenesis and gluconeogenesis. The plasma glucose level rises. Glucocorticoids exert an anti-insulin action in peripheral tissues and make diabetes worse. They have a lipolytic action by increase activity of hormone sensitive lipase in adipose tissue thus increasing plasma free fatty acid levels.

2- Permissive action:

- Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by themselves. This effect is called their **permissive action.**

- Permissive effects include the requirement for glucocorticoids to be present for *glucagon* to exert its lipolytic effects and for *catecholamines* to exert their

lipolytic effects, pressor responses and bronchodilation effects.

3- Effects on the nervous system:

- They maintain normal neuronal excitability. Glucocrticoids excess can cause change in personality, euphoria & psychosis. It also influences mood and behavior.

4- Effect on vascular reactivity:

- They are important for vascular smooth muscle to become responsive to norepinephrine and epinephrine.

5- On kidney functions:

- Glucocrticoids increase glomerular filtration rate (GFR). Also, they decrease the level of vasopressin.

6- On GIT:

- Glucocrticoids increase gastric acid secretion leading to formation of *peptic ulcer*.

7- On blood cells:

Glucocrticoids increase RBCs (polycythemia), platelets, neutrophils While decrease eosinophils, basophils & lymphocytes. *(Immune suppression).*

8- On bone:

- They decrease bone formation (↓ protein synthesis).
- They inhibit osteoblast formation & activity and stimulate osteoclasts.
- They decrease absorption of Ca++ from intestine (anti-vit. D3).
- They increase renal ca++ excretion.

So, prolonged use of cortisol leads to osteoporosis (bone loss).

9- On growth: (Growth retardation)

- They have antigrowth effects by suppressing vitamin D and growth hormone

10- Adaptation to stress:

- The term stress as used in biology has been defined as any change in the environment that changes or threatens to change an existing optimal steady state.
- Most of the stressful stimuli increase ACTH secretion and also activate the sympathetic nervous system.
- The function of circulating glucocorticoids during stress may be maintenance of vascular reactivity to catecholamines. Glucocorticoids are also necessary for the catecholamines to exert their full vasopreesor, lipolytic actions.

- **Glucocorticoids have anti-inflammatory, anti-allergic and immunosuppressive actions.** *So, glucocorticoids can be useful in:*

1- Management of allergic disorders.
2- Management of severe inflammatory conditions.
3- Prevention of organ transplant rejections.

Drawbacks of prolonged use of cortisol:

1. *Atrophy of adrenal gland due to lack of ACTH. (20 mg/d > than 3 weeks)*
2. *Osteoporosis.*
3. *Immune suppression and increased risk of infection.*
4. *Increased blood pressure (hypertension).*
5. *Peptic ulcer.*
6. *Hyperglycemia and secondary dibetes mellitus.*

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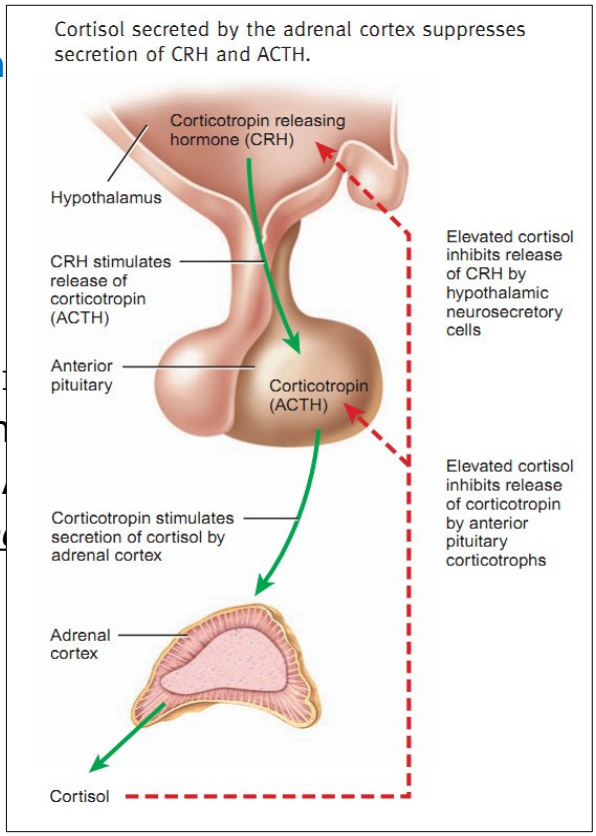
- **Regulation of cortisol secretion:**



1- Hypothalamic pituitary adrenal a

- Corticotropin releasing hormone(CRH) is secreted by the hypothalamus into hypophyseal - portal blood.
- CRH binds to receptors on anterior pituitary.to stimulate ACTH.
- ACTH enhances cortisol secretio
- Cortisol inhibits secretion of CRH from hypothalamus and inhibits secretion of A from anterior pituitary through a *long lo feed back mechanism.*

2- Circadian rhythm:

- ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts. In humans, the bursts are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4:00 AM and 10:00 AM . The bursts are least frequent in the evening.

3- Stress:

- Causes dramatic increase in cortisol secretion .
- Stressful stimuli act on hypothalamus to increase CRH that stimulates ACTH secretion. ACTH increases cortisol secretion.

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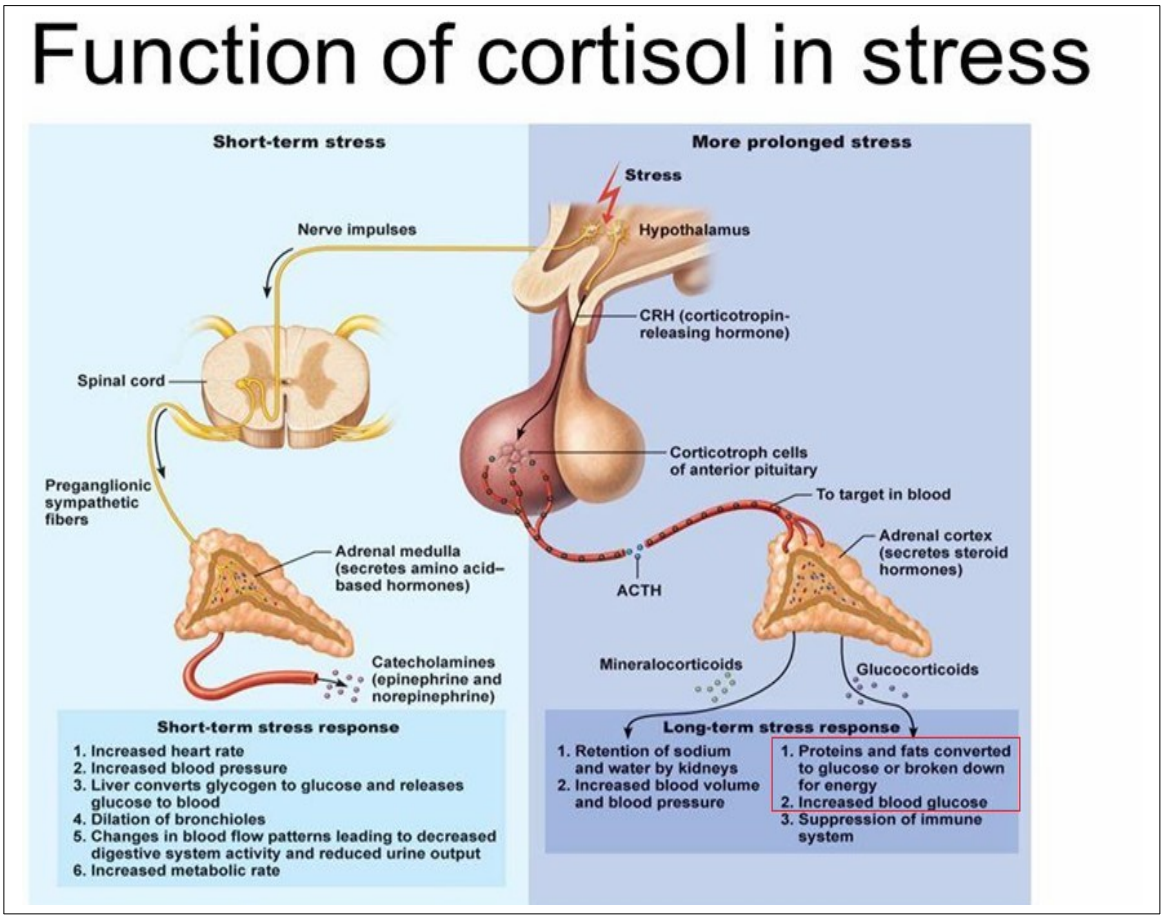

- **Disorders of cortisol hormone secretion :**

  - Excess cortisol secretion which is manifested as Cushing syndrome.
  - It may be ACTH-independent or ACTH-dependent.
  - Deficiency of cortisol hormone: see Addison ’s disease.

Cushing syndrome

- **Causes:**

1- ACTH-independent Cushing syndrome:

a. Glucocorticoid-secreting adrenal tumors.

b. Prolonged administration of exogenous glucocorticoids for diseases such as rheumatoid arthritis.

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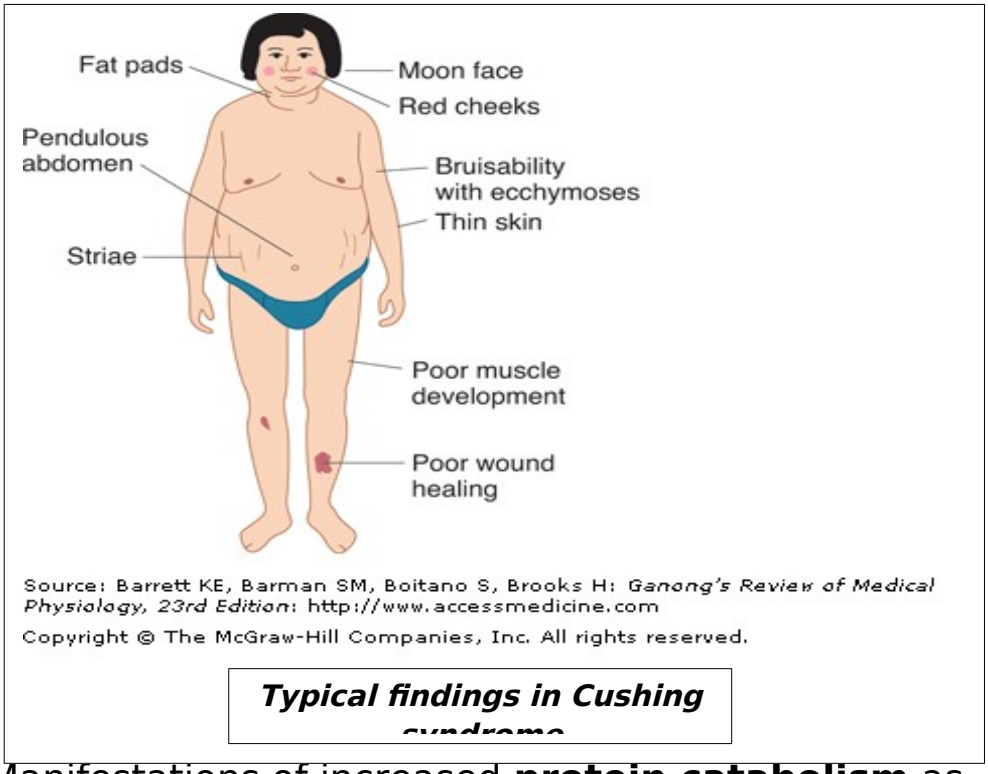
2- ACTH-dependent Cushing syndrome:

- Due to ACTH-secreting tumors of the anterior pituitary gland.
- Cushing syndrome due to anterior pituitary tumors is often called *Cushing disease.*

- **Manifestations:**



Typical findings in Cushing syndrome

1- Manifestations of increased **protein catabolism** as

- *Wasting* of muscles of arms & legs with muscle weakness.
- Loss of collagen support of skin with exposure of underlying capillaries leading to reddish *striae (stria rubra)*.
- Delayed & poor wound healing.
- *Osteoporosis* leading to kyphosis & back pain & bone fractures.

2- Disturbances in fat metabolism:

Redistribution of fat & its deposition in abnormal sites:

a. Rounded face, red with drooping of angle of mouth *"moon face" .*
b. Trunk & abdomen " *trunkal obesity*"
c. Back of neck & interscapular region *"buffalo hump".*

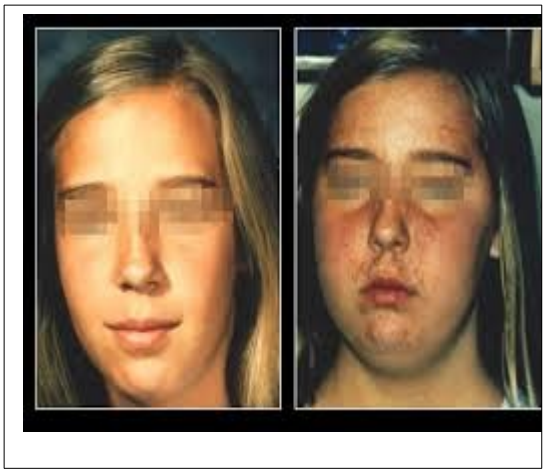
3- Disturbances in CHO metabolism:
- Hyperglycemia and adrenal diabetes

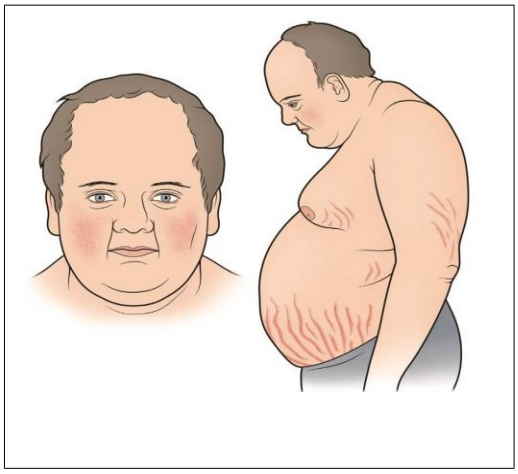
4- Significant mineralocorticoid action leading to salt and water retention and significant K^+ depletion.

5- Mental abnormalities ranging from insomnia, euphoria to frank toxic psychoses.

6- Hypertension due to salt and water retention caused by mineralocorticoid action of excess glucocorticoids together with the direct glucocorticoid effect on blood vessels

7- Osteoporosis as glucocorticoid excess leads to bone dissolution by decreasing bone formation and increasing bone resorption.





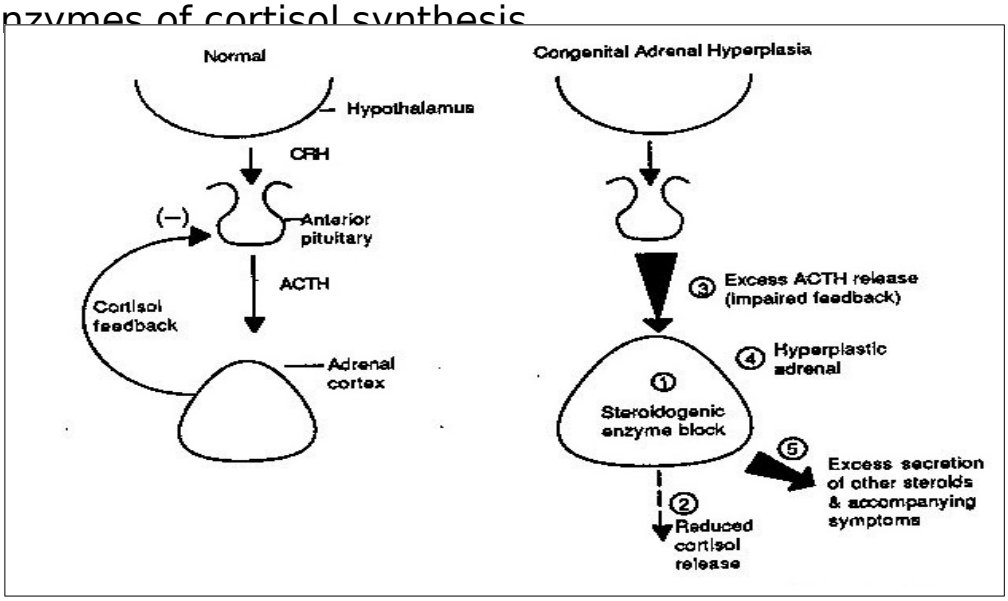
Adrenal sex hormones

- They are secreted by zona reticularis . the secreted androgens are mainly dehydroepiandrosterone (DHEA).

- The amount of sex steroids produced by zona reticularis is insignificant compared to the amounts secreted by the gonads.
- They contribute to the onset of puberty and the appearance of axillary and pubic hair in both males and females.
- In adult women adrenal androgens are responsible for the sex drive.
- Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth. Testosterone from the testes is the most active androgen and the adrenal androgens have less than 20% of its activity.
- Secretion of the adrenal androgens is controlled acutely by ACTH and <u>not</u> by gonadotropins.

Adreno-genital syndrome

- **<u>Cause:</u>** Due to excess adrenal androgen from zona reticularis due to congenital deficiency of one of the enzymes of cortisol synthesis



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- **Manifestations:**

  - Depend on the age and sex of the individual when the hyper activity begins:

Excess adrenal androgen in females		**Excess adrenal androgen in males**	
Before Puberty (birth)	**After puberty**	**Before puberty**	**After puberty**
Pseudo-hermaphrodit (growth of external genitalia of a female in a male pattern)	**Virilism** 1- Hirsutism 2-Enlarged larynx &deep voice 3-Increase muscle bulk 4-Atrophic genitalia& breast	**Precocious pseudopuberty** Development of 2ry sexual characters without testicular activity and without sperm production. (deep voice, beard, enlarged penis, sex derive at an unusually early stage).	no apparent effect because of the already existing male sex characteristic

Adreno-cortical insufficiency

- **Causes:**

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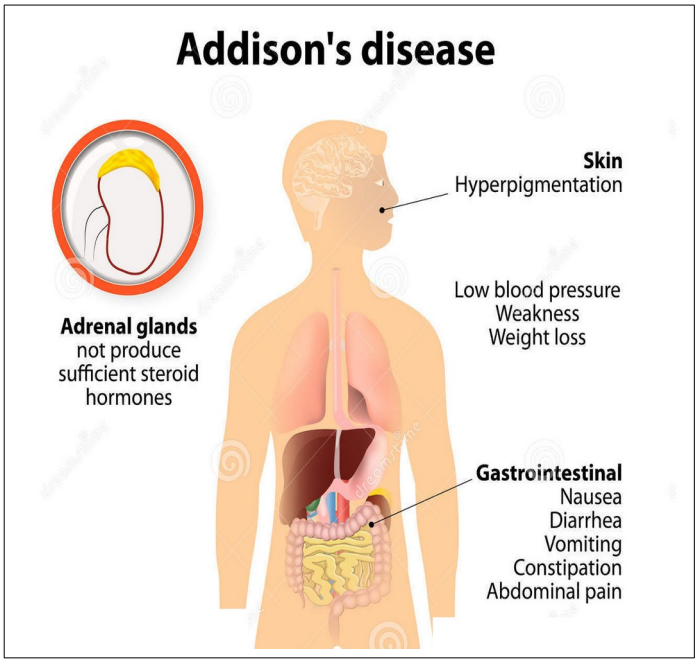
1- **Primary (Addison's disease) due** to either:

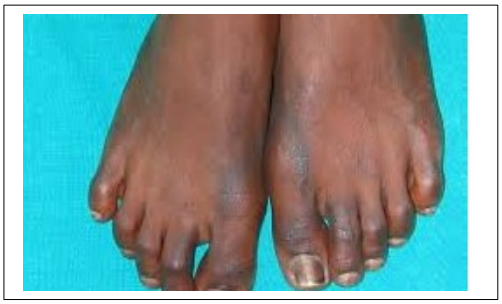
a. Destruction of adrenal gland by auto-immune disease.
b. Destruction of adrenal gland by tuberculosis or cancer.

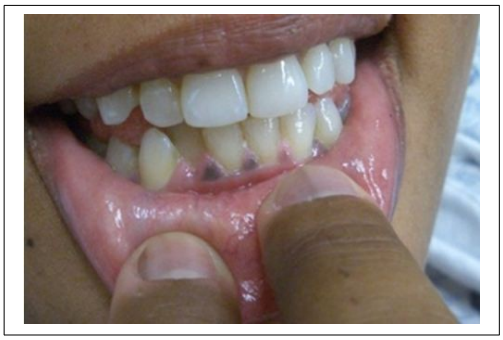
2- **Secondary due to** deficiency of ACTH.

Addison's

- **Cause:** It is primary adrenocortical insufficiency due to Destruction of adrenal gland by auto-immune disease or tuberculosis.







- **Manifestations**: Both cortisol and aldosterone are deficient.

I. *Manifestations of aldosterone deficiency:*

1. Hyponatremia
2. Hypotension (due to Na^+ and fluid depletion).
3. Hyperkalemia causes cardiac arrhythmias.
4. Metabolic acidosis (due to H^+ retention).

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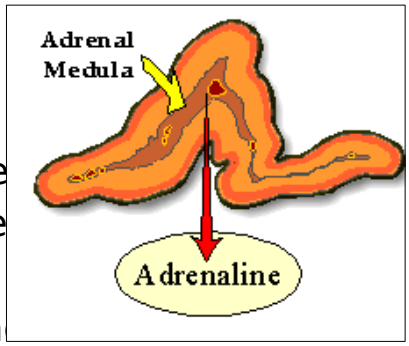
II. Manifestations of cortisol deficiency:

1. Increased pigmentation in skin and mucous membrane results from increased ACTH which has slight MSH-like activity
2. Weight loss, fatigue and muscle weakness due to depression of many metabolic functions of the body.
3. Hypoglycemia due to depressed gluconeogenesis.
4. Poor response to stress.

III. *Manifestations of adrenal androgen deficiency:*

-Loss of pubic and axillary hair.

The adrenal



- It forms the inner part (20% of the gland).
- It is a modified sympathetic ganglia, made up of chromaffin cells which secrete catecholamines (epinephrine and norepine the blood.
- Not essential for life. It reinforces sympath nervous system.
- In most cases the two hormones have very similar effects on their target organs. However, adrenaline is the more potent:
  1- stimulator of the heart rate & strength of contraction
  2- metabolic activities, such as breakdown of glycogen & release of glucose).

While, noradrenaline has great effect on peripheral vasoconstriction and blood pressure.

- **<u>Physiological actions</u>**:

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1-On metabolism:

a. On carbohydrate metabolism:

Catecholamines stimulates glycogenolysis in liver & muscles thus increasing blood glucose level (Hyperglycemic).

Catecholamines inhibit insulin & stimulate glucagon secretion.

b. On fat metabolism:

Catecholamines exert a Lipolytic effect increasing blood levels of free fatty acids.

2-Cardiovascular:

- Norepinephrine and epinephrine both increase the force and rate of contraction of the heart. These responses are mediated by B_1 receptors
- Norepinephrine produces vasoconstriction in most if not all organs via α_1 receptors.

3-CNS: Catecholamines increase alertness.

4-Respiratory system: produces broncho-diltation.

5-GIT & urinary tract: Contraction of sphincters & relaxation of walls of GIT

and urinary tract.

- **<u>Regulation of catecholamine release:</u>**

- Catecholamines secretion by the adrenal medulla is controlled entirely by sympathetic input to the gland.
- Although a number of different factors have been shown to influence adrenal catecholamines secretion, they all act by increasing pregangionic sympathetic impulses to the adrenal medulla. e.g.:

1. Increase catecholamine secretion in response to **cold** (due to its calorigenic action).
2. Severe **hypoglycaemia** and stressful states stimulate the hypothalamus directly which in turn stimulates the adrenal medulla.

3. **Hemorrhage** is a potent stimulus of adrenal medullary secretion (due to its vasoconstrictor effect).

Note:

*Most adrenal medullary tumors **(pheochromocytomas)** secrete norepinephrine, or epinephrine, or both, and produce sustained hypertension. However, 15% of epinephrine-secreting tumors secrete this catecholamine episodically, producing intermittent bouts of palpitations, headache, glycosuria, and extreme systolic hypertension.*